Exhibit L. Written Post-Hearing Comments

Comments received during the Post-Hearing Comment Period (April 7, 2023, to April 26, 2023) and MDH responses

L.1.a.i. Topic: PFAS
Commenter: Greg Johnson, Metropolitan Council
Date: April 7, 2023

L.1.a.ii. Minnesota Department of Health's Response
Date: April 26, 2023

L.1.b.i. Topic: HRL Enforcement -
Commenter: Jean Wagenius (Former State Representative)
Date: April 24, 2023

L.1.b.ii. Minnesota Department of Health's Response
Date: April 26, 2023

L.1.c.i. Topic: Nonylphenol
Commenter: Barbara Losey, Alkylphenols & Ethoxylates Research Council)
Date: April 26, 2023

L.1.c.ii. Minnesota Department of Health's Response
Date: April 26, 2023

L.1.d.i. Topic: Imidacloprid
Commenter: William Reeves, Bayer Crop Science
Date: April 26, 2023

L.1.d.ii. Minnesota Department of Health's Response
Date: April 26, 2023

L.1.a. Written Comment: Post Hearing Comments – PFAS

L.1.a.i. Comment
Date: April 7, 2023
Chemical: PFAS
Commenter: Metropolitan Council

L.1.a.ii. Minnesota Department of Health's Preliminary Response
Date: April 24, 2023

METROPOLITAN
COUNCIL

March 22, 2023

Ms. Nancy Rice
Minnesota Department of Health
Health Risk Assessment Unit
P.O. Box 64975
St. Paul, MN 55164-0975

Subject: Comments on Minnesota Department of Health Proposed Health Risk Limits for PFAS

Dear Ms. Rice:

The Metropolitan Council appreciates this opportunity to comment on the Minnesota Department of Health's (MDH) proposed amendments to its recommended Health Risk Limits (HRLs) for drinking water. Metropolitan Council promotes sustainable water supplies and high-quality drinking water for all consumers within the Twin Cities Metropolitan Area.

MDH proposes amendments to the HRL Rules approximately every two years. This allows new and updated human health-based water guidance values to be considered for adoption into rule. The water guidance values for the contaminants listed on MDH's website at Health Risk Limits Rules for Groundwater Rules Amendments - Contaminants - MN Dept. of Health (state.mn.us) are under consideration for the next HRL Rules amendment process. MDH has also published recommended health risk limits and an overall health index (HI) for six PFAS compounds, including PFBS, PFBA, PFHxS, PFHxA, PFOA, and PFOS. The current amendments include the PFAS compounds of PFBS, PFHxS, and PFHxA. The list of contaminants does not include amendments for PFBA, PFOA, or PFOS.

On June 15, 2022, the Environmental Protection Agency (EPA) tightened its recommended lifetime interim health advisory levels for two PFAS compounds that are globally widespread contaminants in drinking water, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). For PFOA, the recommended interim health advisory level is 0.004 part per trillion (ppt) and for PFOS, 0.02 ppt. These levels are dramatically lower than the 70 ppt that the EPA recommended in 2016 for these two PFAS compounds. In addition, these levels are significantly lower than MDH's current recommended levels of 35 ppt for PFOA and 15 ppt for PFOS.

EPA proposed a National Drinking Water Regulation for PFOA and PFOS on March 14th, 2023. This proposed regulation will include a non-enforceable Maximum Contaminant Level Goal (MCLG) and an enforceable standard, or Maximum Contaminant Level (MCL). Under the Safe Drinking Water Act, public water systems are required to meet MCLs for contaminants. Public water systems are not required to meet MCLGs. EPA proposed regulating PFOA and PFOS as "individual contaminants," which would be regulated at four parts per trillion.

In addition to EPA proposing MCLs for PFOA and PFOS, EPA also announced on March 14th, 2023, that the Biden administration would establish legally enforceable levels for four additional PFAS compounds known to occur in drinking water and will build on previous EPA proposals and regulations. Under the

Metropolitan Council (Regional Office & Environmental Services)
390 Robert Street North, Saint Paul, MN 55101-1805
P 651.602.1000 | F 651.602.1550 | TTY 651.291.0904
metrocouncil.org

proposal, the four other PFAS compounds would be deemed "a mixture" and would limit the combined levels of those substances in water. Public water systems would also have to notify the public and work to reduce contamination if levels exceed the proposed regulatory standards according to EPA.

Multiple communities in the Metropolitan Area have been impacted by PFAS contamination based on the current recommended health advisory levels established by MDH. These communities will likely be impacted significantly more with EPA's stringent proposed MCLs for PFOA and PFOS and the four additional PFAS compounds that EPA is seeking to regulate. Additional communities that currently have acceptable health index values, based on current guidelines, may also be impacted by the upcoming PFAS MCLs for the very first time. Metropolitan Council notes that the current MDH health advisory levels for PFOA and PFOS are significantly higher than EPA's current recommended interim health advisory levels that will likely become enforceable MCLs in the near future. Because EPA's proposed MCLs for PFOA and PFOS are much lower than the current MDH recommended levels, the region's water suppliers may be significantly impacted. The new MCLs to be established by EPA for the four additional PFAS compounds could have additional impact on communities.

The Met Council supports partnering with state agencies, water suppliers and stakeholders to address PFAS contamination across the water cycle. We suggest this partnership start with understanding, together, how PFAS impacts water quality, public health, ecosystem health, and wastewater in order to put forth the most effective ways to address PFAS in the state and the Twin Cities region. In its water supply planning role, the Met Council is committed to working with MDH and the region's water suppliers to better understand the implications to water supplies and evaluate shared solutions to help water suppliers address PFAS. If you have any questions on these comments, please contact Greg Johnson, Principal Engineer, at the Metropolitan Council at 651-602-1016 or Greg.Johnson@metc.state.mn.us.

Sincerely,

Sam Paske

Sam Paske (Mar 23, 2023 08:51 CDT)

Sam Paske
MCES, Assistant General Manager

DEPARTMENT OF HEALTH

Protecting, Maintaining and Improving the Health of All Minnesotans

April 24, 2023

Sam Paske
MCES, Assistant General Manager
Metropolitan Council
390 Robert Street North
St. Paul, MN 55101

Re: Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, and Part 7860; Revisor's ID Number RD4587, OAH Docket No. 5-9000-38941

Dear Sam Paske:

Thank you for your comments of March 22, 2023, on the proposed Health Risk Limits Rules Amendments via the Office of Administrative Hearing's Rulemaking eComments website.

You correctly note that the current amendments include the PFAS compounds of PFBS, PFHxS, and PFHxA but does not include amendments for PFBA, PFOA, or PFOS. A Health Risk Limits (HRLs) for PFBA were promulgated and adopted as rule in August 2018. Since there are no new toxicity or methodological updates that would result in changes to the 2018 HRL values, PFBA is not part of the current proposed rules revision. MDH withdrew proposed changes to PFOA and PFOS and initiated a re-evaluation last fall focusing on assessing epidemiological (human) study data. This re-evaluation was, in part, initiated to consider the findings from several recent reviews, including the US EPA. We expect that PFOA and PFOS will be included in the next round of rulemaking.

MDH supports US EPA's mixtures approach for assessing the presence of multiple contaminants in drinking water. The HRL Rules have incorporated an additivity model for assessing multiple contaminants that affect the same health endpoints since the inception of the HRL rules in 1993. For more details on how additivity is calculated in Minnesota for six PFAS, please see our 2009 SONAR (https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=2), page 69.

PFAS science is a very active area of research and MDH acknowledges the challenges faced by impacted communities. To keep up with all health-based guidance development, please consider joining our GovDelivery subscription email notification. To join, please visit Health Risk Limits Rules for Groundwater Overview and Links (https://www.health.state.mn.us/hrlrules.html) and provide your email address in the "Get Email Updates" box at the bottom of the page.

Sincerely,

Sarah Fossen Johnson
Manager, Environmental Surveillance and Assessment Section
Minnesota Department of Health
Environmental Health Division
651-201-4899
health.risk@state.mn.us
www.health.state.mn.us

L.1.b. Written Comment: Post-Hearing Comments- HRL Enforcement

L.1.b.i. Comment
Date: April 24, 2023
Chemicals: HRL Enforcement
Commenter: Jean Wagenius

L.1.b.ii. Minnesota Department of Health's Response
Date: April 26, 2023

38941 Minnesota Department of Health Notice of Hearing (Post-Hearing Comment Period)

Closed Apr 26, 2023 · Discussion · 5 Participants · 1 Topics · 8 Answers · 3 Replies · 0 Votes

5	1	8	3	0
PARTICIPANTS	TOPICS	ANSWERS	REPLIES	VOTES

SUMMARY OF TOPICS

SUBMIT A COMMENT

8 Answers · 3 Replies

Important: All comments will be made available to the public. Please only submit information that you wish to make available publicly. The Office of Administrative Hearings does not edit or delete submissions that include personal information. We reserve the right to remove any comments we deem offensive, intimidating, belligerent, harassing, or bullying, or that contain any other inappropriate or aggressive behavior without prior notification.

Greg Johnson · Citizen · (Postal Code: unknown) · Apr 07, 2023 3:09 pm

0 Votes

Comments from the Metropolitan Council are attached.

Response:

Nancy Rice · Citizen · (Postal Code: unknown) · Apr 26, 2023 11:15 am

A response from Minnesota Department of Health has been added.

Jean Wagenius · Citizen · (Postal Code: unknown) · Apr 24, 2023 6:22 pm

0 Votes

In the Matter of the Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, and Part 7860;
Revisor's ID Number 4587
OAH Docket No. 5-9000-38941

I appreciate the opportunity to respond to the Department of Health's letter dated March 31, 2023.

In the letter MDH reasserts its position that Health Risk Limits are not enforceable citing its interpretation of the definition in Minn. Stat. 103H.005, subd. 5. But this definition does not preclude MDH from enforcing HRLs. Moreover, the definition read together with the other governing statutes make it clear that HRL's are enforceable by MDH.

I gladly support the proposed HRLs that “include a reasonable margin of safety to adequately protect the health of infants, children, and adults.” Minn. Stat 144.0751. But I ask the Administrative Law Judge to reject MDH’s assertion that HRLs promulgated in this rule making are “non-regulatory” and find that the HRLs have the force and effect of law and thus are enforceable by MDH.

Health Risk Limits were included in the 1989 Groundwater Protection Act. The operative language in Minn. Stat. 103H.201 Subd. 2 (a) says “(h)ealth risk limits shall be adopted by rule.” At that time, the Administrative Procedure Act had been in law for decades. Minn. Stat. 14.38 provides for the effect of adopted rules. Subdivision 1 states that “(e)very rule…shall have the force and effect of law.” The legislature clearly intended that HRLs would have the force and effect of law.

Moreover Subdivision 2 (b) reinforced that intention when the legislature gave the commissioner the authority to adopt health risk limits notwithstanding chapter 14 if the commissioner determines that “emergency conditions exist and the public health and welfare require the health risk limits to be adopted as soon as possible.…” The legislature gave that authority with the expectation that a HRL would need to be enforced as soon as possible.

In its SONAR MDH cites the Groundwater Protection Act of 1989 as authority to adopt HRLs: “(i)f groundwater quality monitoring results show that there is a degradation of groundwater, the commissioner of health may promulgate health risk limits under subdivision 2.” SONAR p. 2

The Department also cites Minn. Stat. 144.0751 Health Standards which provides the outcome that a HRL must achieve and the criteria to be satisfied to reach that outcome. Specifically, a HRL must “include a reasonable margin of safety to adequately protect the health of infants, children, and adults” for each of the following “ reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner.” Minn. Stat. 144.0751 was enacted in 2001, after the Groundwater Protection Act.

MDH applies the Health Standards law when it creates a HRL and then uses it to defend its proposed rules. In each of the responses to HRLs contested by members of the chemical industry MDH points out that it is responsible under law to “include a reasonable margin of safety to adequately protect the health of infants, children, and adults.…”

MDH clearly understands that the Health Standards law governs its creation of HRLs. The Health Standards law does not provide for any exceptions that would give the commissioner the discretion to not enforce HRLs once they have been promulgated in a rule making process. Yet by refusing to enforce HRLs and telling others that they don’t need to follow them, MDH has chosen to make the Health Standards law meaningless. The result: the Health Standards law that was designed to protect the health of infants and children does not protect the health of infants, children, or adults according to MDH.

MDH also ignores the statute setting out the responsibilities of the commissioner of health. Minn. Stat. 144.05 says the commissioner “shall be responsible for the development and maintenance of an organized system of programs and services for

protecting, maintaining, and improving the health of the citizens. This authority shall include…(3) establish and enforce health standards for the protection and the promotion of the public's health.…." (emphasis added.) HRLs comply with Minn. Stat. 144.0751 HEALTH STANDARDS and are clearly standards to be enforced under Minn. Stat. 144.05.

The MDH enforces the federal Safe Drinking Water Act including the standards and treatment techniques that apply to public water systems in order to protect drinking and source water. SONAR p 80. EPA-derived MCLs are federal standards adopted for the regulation of public drinking water in Minnesota. "EPA has developed standards for 91 chemicals, with the most recent value developed in 2001….As a result, most MCLs were developed using outdated methods based only on adult intakes and body weight."SONAR. P 80. The more specific Health Standards law became effective in 2001. And since 2001 additional chemicals have been found in groundwater in Minnesota.

The Groundwater Act authorizes MDH to adopt HRLs by rule for contaminants found in Minnesota groundwater. MDH creates a HRL only when a contaminant is found in groundwater. MDH states that its HRLs meet the outcome and criteria of the Health Standards act. MDH acknowledges that 75% of Minnesotans use groundwater for drinking water. Nonetheless MDH asks the Administrative Law Judge to agree with it when it says that the legislature never intended that MDH protect drinking water by enforcing health standards for drinking water. MDH asks for this result: MDH would continue to enforce outdated federal standards but not enforce new or updated protective HRL standards for chemicals found in Minnesota's groundwater. The Judge should reject MDH's assertion and find that HRLs have the force and effect of law and are enforceable by MDH.

The law is clear. It is supported by well accepted public policy and MDH's own mission statement. The government's first responsibility is keeping citizens safe. That includes making sure drinking water is safe, safe for every Minnesotan. Groundwater that is drinking water is not unsafe uniformly across the state. Only parts of the state are vulnerable to groundwater contamination and unsafe drinking water. Equity, also, tells us that Minnesotans living in areas vulnerable to drinking water contamination should have safe drinking water just like the rest of Minnesotans.
Jean Wagenius
4804 11th Avenue S.
Minneapolis
612-822-3347

Response:
Nancy Rice · Citizen · (Postal Code: unknown) · Apr 26, 2023 4:14 pm
A response from Minnesota Department of Health has been added.

Barbara Losey · Citizen · (Postal Code: unknown) · Apr 26, 2023 7:59 am
0 Votes

The Alkylphenols & Ethoxylates Research Council (APERC) submits these post-hearing comments to oppose proposed amendments to rules governing Health Risk Limits (HRLs) for
groundwater, Minnesota Rules, Ch. 4717.7860 Subpart 13a, p-Nonylphenol (pNP), also called 4-Nonylphenol (4NP). These comments are submitted under discussion 38941 to

38941 Minnesota Department of Health Notice of Hearing (Post-Hearing Comment Period)

Closed Apr 26, 2023 · Discussion · 5 Participants · 1 Topics · 8 Answers · 3 Replies · 0 Votes

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OAH Docket No. 5-9000-38941. Specifically, APERC opposes the proposed sub-chronic and chronic HRLs for pNP for the reasons discussed in the attached comments.

Response:

Nancy Rice · Citizen · (Postal Code: unknown) · Apr 26, 2023 4:11 pm
A response from Minnesota Department of Health has been added.

William Reeves · Citizen · (Postal Code: unknown) · Apr 26, 2023 2:15 pm
0 Votes

Follow up comments from Bayer Crop Science

Nancy Rice · Citizen · (Postal Code: unknown) · Apr 26, 2023 4:29 pm
0 Votes

A response from Minnesota Department of Health has been added.

April 26, 2023

Jean Wagenius
4804 11th Avenue S.
Minneapolis, MN 55417

Dear Jean Wagenius:

We received your comment dated April 24, 2023, that reiterates your opinion that Administrative Law Judge Mortenson must "find that HRLs have the force and effect of law and are enforceable by MDH." You make this assertion, largely based on your interpretation of provisions within sections of Minnesota Statutes that make no reference to HRLs nor any section of the chapter authorizing them. You made this same claim in your earlier comment on this rule, dated March 4, 2023. Accordingly, we refer you to our March 31, 2023, response to your first comment. For your convenience, we repeat the relevant portion of that response here:

> The legislature . . . specifically requires HRLs to be set in rule and defines them, not as directly enforced limits on any particular party's conduct, but as baselines for operationalizing the point where a concentration of a given substance becomes a potential health risk (103H.005, subd. 3). That MDH has general statutory authority to regulate environmental health hazards does not prohibit MDH from complying with a clear directive from the legislature to set HRLs in rule. In more than 20 years MDH has not interpreted the statute this way, nor has any administrative law judge during previous rulemakings.

Over the course of 8 previous rulemakings, the department has adopted at least 146 HRLs through Democratic, Republican, and Independent administrations—each with their own MDH commissioners and dozens of MDH employees. To be clear, MDH has never been required to enforce or declare an intention to enforce HRLs as a prerequisite for the approval of its HRLs and its ultimate compliance with the statutory mandate that "[h]ealth risk limits shall be adopted by rule." (103H.201, subd. 2(a)).

As you likely know, part of what makes a HRL a powerful public health tool is that it presents no economic impact on stakeholders. If HRLs were regulatory, a complex consideration of how much it would cost to enforce each HRL would need to be made alongside its establishment or revision. This would slow down and complicate MDH's ability to set these health-based standards. Thus, MDH's longstanding approach to HRLs accomplishes exactly what your comment seems to seek: Better health protection for people who drink water in Minnesota.

That MDH itself does not enforce HRLs does not mean, however, that they are rendered meaningless or ineffective. In addition to authorizing MDH's adoption of HRLs into rule, Minnesota Statutes, chapter

103H, also authorizes the Minnesota Department of Agriculture (MDA) and the Minnesota Pollution Control Agency (MPCA) to adopt water resource protection requirements (WRPR) into rule. (§ 103H.275, subd. 2). In furtherance of your desire that HRLs be enforced, the legislature in fact directed that WRPRs "must be . . . designed to prevent . . . pollution from exceeding the health risk limits . . . ." (§ 103H.275, subd. 1(c)(2)). Consistent with other statutory frameworks for enforcement of standards, the legislature also provides MDA and MPCA with extensive guidance for how it should adopt and enforce these regulations, including by providing remedies for their violation, something the chapter lacks regarding HRLs. (*Compare*, § 103H.201 (authorizing and directing MDH's adoption of HRLs) *with*, §103H.275 (authorizing and directing MDA and MPCA's adoption of WRPRs)).

Many other regulatory programs use HRLs, as well. For example, the Drinking Water Protection Section's main goal is to enforce the federal Safe Drinking Water Act (SDWA). Over the past twenty years, staff in that section have worked closely with the Health Risk Assessment Unit staff to develop a process for addressing unregulated contaminants (HRLs) at public water supplies. This is most obvious with work on PFAS, which, for example, has led to a data portal that all Minnesotans on municipal water can view their sampling results. There have also been multiple sampling efforts by MDH, MDA, and MPCA for private well owners over the last twenty years that have used HRLs as guidance because there is no SDWA for private wells. As you can see, the HRLs do not sit unused. In fact, year after year we seek funding for more staff because we provide technical assistance to other state and local agencies seeking to use HRLs more frequently.

Respectfully,

Sarah Fossen Johnson
Manager, Environmental Surveillance and Assessment Section
Minnesota Department of Health
Environmental Health Division
651-201-4899
health.risk@state.mn.us
www.health.state.mn.us

L.1.c. Written Comment: Post-Hearing Comments- Nonylphenol

L.1.c.i. Comment
Date: April 26, 2023
Chemicals: Nonylphenol
Commenter: Alkylphenols and Ethoxylates Research Council (APERC)

L.1.c.ii. Minnesota Department of Health's Preliminary Response
Date: April 26, 2023

APE RESEARCH COUNCIL 1250 CONNECTICUT AVENUE, NW, SUITE 700, WASHINGTON, DC 20036
(202) 539-4060 INFO@APERC.ORG

Comments of the Alkylphenols & Ethoxylates Research Council

In the Matter of the Proposed Amendments
to Rules Governing Health Risk Limits for Groundwater,
Minnesota Rules, Ch. 4717.7860 Subpart 13a
p-Nonylphenol (4-Nonylphenol)
(Discussion 38941)

Submitted to the Office of Administrative Hearings under eComments
OAH Docket No. 5-9000-38941

April 26, 2023

The Alkylphenols & Ethoxylates Research Council (APERC) submits these post-hearing comments to oppose proposed amendments to rules governing Health Risk Limits (HRLs) for groundwater, Minnesota Rules, Ch. 4717.7860 Subpart 13a, p-Nonylphenol (pNP), also called 4-Nonylphenol (4NP). These comments are submitted under discussion 38941 to OAH Docket No. 5-9000-38941. Specifically, APERC opposes the proposed sub-chronic and chronic HRLs for pNP for the reasons discussed below.

Background

APERC is a North American organization whose mission is to promote the safe use of alkylphenols, including pNP through science-based research and outreach efforts, within the framework of responsible chemical management.[1] For more than thirty years, APERC and its member companies have been actively engaged in the conduct and review of studies on the toxicological effects of pNP and related compounds.

APERC submitted detailed written comments on March 8, 2023 to the docket in the matter of the proposed HRLs for pNP. Previous comments and a presentation that were provided as preregulatory information to the MN Department of Health (MDH) were included as attachments to those comments. Those comments primarily responded to MDH's focus on the selection of mineralization in male rat kidneys as the Critical Effect for the derivation of subchronic and chronic HRLs for pNP.

APERC thanks the MDH for the considerable time and effort they put into the development of the HRLs for pNP and for their professionalism accepting, carefully considering, and responding

[1] APERC member companies include: The Dow Chemical Company, Dover Chemical Corporation, and SI Group, Inc.

to our comments throughout this process. The topic of assessing renal effects observed in toxicology studies is complex and we appreciate the effort MDH undertook to do this with respect to pNP.

During the public administrative hearings on April 5th and 6th, 2023 Judge James Mortenson outlined the following three key issues under consideration during the public administrative hearing.

1. Does the Agency have legal authority to adopt the rules?
2. Has the Agency fulfilled all relevant legal and procedural requirements to promulgate the rules?
3. Has the Agency demonstrated the need and reasonableness of each portion of the proposed rules?

APERC's comments below assert that MDH has not sufficiently demonstrated reasonableness (item 3 above) in its selection of renal effects (mineralization) as the Critical Effect for derivation of the subchronic and chronic HRLs for pNP. The Minnesota Administrative Procedure Act (APA), Minnesota Statutes, chapter 14, requires MDH to justify the need to amend the existing HRL rules and the reasonableness of the amendments in a Statement of Need and Reasonableness (SONAR). (See Minn. Stat. § 14.131). For the subchronic and chronic HRLs for pNP, MDH has selected a Point of Departure (POD) based on their interpretation that renal mineralization seen in male rats in a study conducted by the National Toxicology Program (NTP) in 1997 and published by Chapin et al., 1999 is an "adverse" effect. [2,3] This interpretation is unreasonable for the reasons discussed in Section 1.0 below. APERC's recommended Critical Effect, POD and derivation of the HRL for pNP are provided in Section 2.0 below.

1.0 The evidence for adversity in the selection of renal mineralization in young male rats as the Critical Effect for pNP is weak and not consistent with the SONAR definition of "adverse"; therefore, selection of this as a Critical Effect for pNP is not reasonable.

The January 2023 SONAR related to this rulemaking to amend HRLs includes the following definitions in Appendix A "Glossary of Terms Used in Risk Assessment". [4]

- **Adverse Effect**: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

[2] National Toxicology Program (NTP). (1997). Final Report on the Reproductive Toxicity of Nonylphenol (CAS #84852-15-3) (Vol. RACB No. 94-021, pp. 576): National Institute of Environmental Health Sciences
[3] Chapin, R. E., Delaney, J., Wang, Y., Lanning, L., Davis, B., Collins, B., Mintz, N., & Wolfe, G. (1999). The effects of 4-nonylphenol in rats: a multigeneration reproduction study. *Toxicol Sci*, **52**(1), 80-91. This is the peer-reviewed publication that summarizes the NTP study referenced above.
[4] Minnesota Department of Health (MDH) (2023, January 26) Statement of Need and Reasonableness (SONAR): Proposed Amendments to the Rules on Health Risk Limits for Groundwater (Minnesota Rules, Chapter 4717, Parts 7500, 7850, and 7860).

- **Benchmark Dose (BMD**): Dose or concentration that produces a predetermined change in the response rate of an adverse or biologically meaningful effect.
- **Critical effect(s):** The health effect or health effects from which a non-cancer toxicity value is derived; usually the first adverse effect that occurs to the most sensitive population as the dose increases.

Based on these definitions, both the Critical Effect and the Benchmark Dose should be based on adverse effects, which are defined as "affecting the performance of the whole organism or reducing an organism's ability to respond to an additional environmental challenge".

The July 2008 MDH SONAR for HRLs, which describes the process for derivation of HRLs provides the following additional clarification for what constitutes "adverse":

> "…for the purpose of the MDH-derived HRLs, an adverse health effect is identified as the organ, tissue, or system in which the effect is manifested or as the occurrence of cancer" and "in order to constitute a toxic effect, several criteria must be satisfied" one of which is that "the effect observed must be either adverse or biologically meaningful."[5]

> 1.1 pNP does not exhibit a constellation of kidney effects that together indicate an adverse impact; or framed under the SONOR definition, a constellation of effects that "affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge."

The focus of MDH's efforts for pNP has been on understanding and applying data related to potential kidney effects. Assessment of toxicity in kidney is a multifaceted topic. Rodent (rat and mouse) toxicology studies feature many endpoints, not all of which are necessarily adverse individually, which can provide insight into toxicity. These endpoints include:

> *Kidney weights* – organ weights often are the most sensitive endpoint associated with toxicity. Although they may not indicate a specific mechanism, they are a good indicator that something may be amiss. Modest changes in kidney weights may occur in toxicology studies without histopathological evidence of cellular damage. It is uncommon that this is the only change noted in the presence of true kidney toxicity. Kidney weights were determined in almost all studies with pNP and with one exception of a ~10% increase in kidney weights in a study by Tyl, 2006, no treatment-dependent changes in weights were noted at the lowest dose in any of the studies. [6]

[5] Minnesota Department of Health (MDH). (2008, July 11). Statement of Need and Reasonableness (SONAR): Proposed Amendment to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, 4717.7810 *et seq.*
[6] Tyl, R.W., Myers, C.B., Marr, M.C., Castillo, N.P., Seely, J.C., Sloan, C.S., Veselica, M.M., Joiner, R.L., Van Miller, J.P., & Simon, G.S. (2006). Three-generation evaluation of dietary para-nonylphenol in CD (Sprague Dawley) rats. *Toxicological Sciences*, 92, 295-310

Clinical pathology – this refers to data that one obtains by analyzing components of blood, most commonly blood urea nitrogen (BUN) and serum creatinine. Elevations in either or both often point to alterations in kidney function.

Although the Chapin, 1999 study on pNP did not assess these parameters, a 90-day pNP study by Cunny et al., 1997 did and reported no treatment-related changes either BUN or serum creatinine.[7, 8]

Histopathology – The careful examination of tissue slides prepared from animals exposed and not exposed to the chemical of interest is an important factor. In addition to the incidence of effects (the number of animals exhibiting a change in renal histopathology) it's important to consider the severity of such results in determining when an observed endpoint is adverse. In the NTP study on pNP reported by Chapin,1999, essentially all the histopathological changes, regardless of dose, were described in by the authors as being "slight to mild."

In considering the constellation of possible kidney effects from pNP in the Chapin, 1999 study, as well as other studies: no treatment related effects were seen in clinical pathology; essentially all the histopathological changes in the Chapin, 1999 study are of "slight to mild" severity; and with one exception, no treatment-dependent changes in kidney weights were noted at the lowest dose in any of the other studies on pNP. Therefore, with possible exception of effects at the higher doses, pNP is *unlikely* to induce adverse effects, as defined by the SONAR for HRLs, that would affect the performance of the whole organism (in this case the rat) or reduces an organism's ability to respond to an additional environmental challenge.

1.2 MDH's interpretation of kidney effects in the Chapin, 1999 study is unreasonable as it is inconsistent with scientific guidance on the relevance of the mineralization findings for pNP in rats, and does not fit the SONAR definition of "adverse".

APERC's previous comments noted that "the renal mineralization in rats, as seen at lowest dose in the NTP, 1997\Chapin et al, 1999 study, is common and not considered adverse in rat pathology; its occurrence at the lowest dose in this study was in isolation from other true adverse effects and should not be viewed as a treatment-related adverse effect and should not be the Critical Effect from which a POD is calculated for pNP". [9] Furthermore, the comments provided significant expert citations from pertinent publications that explain that rats are widely known to have a high rate of various spontaneous kidney lesions, including mineralization. Mineralization seen in the rat kidney at the lowest dose in the Chapin, 1999 rat study should not be considered

[7] Chapin, (1999).
[8] Cunny, H.C., Mayes, B.A., Rosica, K.A., Trutter, J.A., & Van Miller, J.P. (1997). Subchronic toxicity (90-day) study with para-nonylphenol in rats. Regulatory Toxicology and Pharmacology, 26 (2), 172-178.
[9] Alkylphenols & Ethoxylates Research Council (2023, March 8). Comments in the Matter of the Proposed Amendments to rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Ch. 1717.7860 Subpart 13a. Initial Comment Period. Discussion 38941.

an adverse effect and should not serve as the Critical Effect from which to calculate a POD for HRLs.

In its response to APERC's comments, MDH explained its view that "Renal mineralization observed in Chapin 1999 is adverse because it is occurring prematurely in young male rats and *might* be associated with renal degeneration" and "Mineralization observed at the lowest dose *may* be a marker of more severe effects and *may* also be considered adverse". [10] (Emphasis added). It is worth noting that expert guidance for toxicologic pathology in the rat kidney advises that "mineralization occurs more often in female than male rats because of its relationship with estrogen levels, but is found in both very young and old animals." [11]

It is APERC's view that MDH's interpretation of kidney effects reported by Chapin, 1999 is not a reasonable interpretation of "adverse" as it is inconsistent with scientific guidance on the relevance of the mineralization findings for pNP in rats, is inconsistent with the findings in the cited source study, and does not fit the SONAR definition of "adverse". [12, 13] SONAR defines "adverse effect" as "a biochemical change, functional impairment, or pathologic lesion that *affects* the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge. It does not say that effects that "*might* be associated" with another effect or "*may* be considered a marker" are adverse. Most important, the National Toxicology Program's (NTP's) Atlas to the Kidney states that: "In general, these deposits have no pathologic significance" in reference to renal mineralization lesions. [14]

1.2.1 Slight to mild histopathological findings, related to kidney lesions in young male rats as described in Chapin, 1999, which are generally viewed to have no pathologic significance, do not meet the level of "adverse" as defined in the SONARs for HRLs. [15, 16]

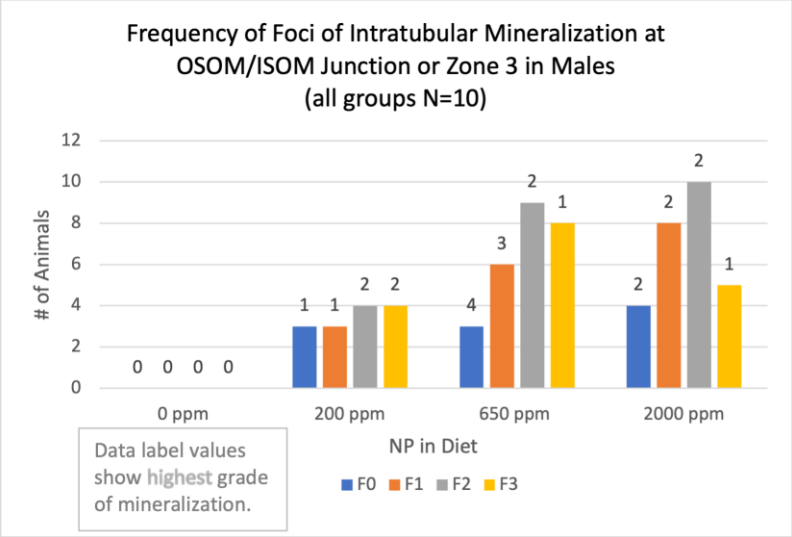
The text in Chapin, 1999 provided qualitative descriptions of "slight to mild" for the kidney mineralization effects seen from pNP in rats. However, no numerical score were provided in this study. Nonetheless an expert review of the histopathology slides from the NTP 1997\Chapin,

[10] Minnesota Department of Health (MDH) (2023, March 31) Letter to Alkylphenols & Ethoxylates Research Council in Response to Comments.
[11] Hard, G.C., Alden, C.L, Bruner, RH.G., Frith, C.H., Lewis, R.M. Owen, R.A., Krieg, K and Durchfeld-Meyer, B. (1999). Non-proliferative lesions of the kidney and lower urinary tract in the rat, URG-1. Guides for Toxicologic Pathology. STP/ARP/AFIP, Washington, DC
[12] MDH. (2008, July 11).
[13] MDH. (2023, January 26).
[14]Schmidt CW. National Toxicology Program (NTP). (2014). Non-Neoplastic Lesion Atlas: a new tool for toxicologic pathology. *Environ Health Perspect.* 122(3): A76-9. doi: 10.1289/ehp.122-A76. PMID: 24583717; PMCID: PMC3948027.
[15] MDH. (2008, July 11).
[16] MDH. (2023, January 26).

1999 study by Dr. Gordon Hard produced numeric scores, which are presented in Figures 1 and 2 below.[17]

Figures 1 and 2 summarize the severity of kidney mineralization in male and female rats in the NTP\Chapin, 1999 study as scored by expert review in Hard, 1998. The highest mineralization score (i.e., 1-4) is noted above the bar for each test group.

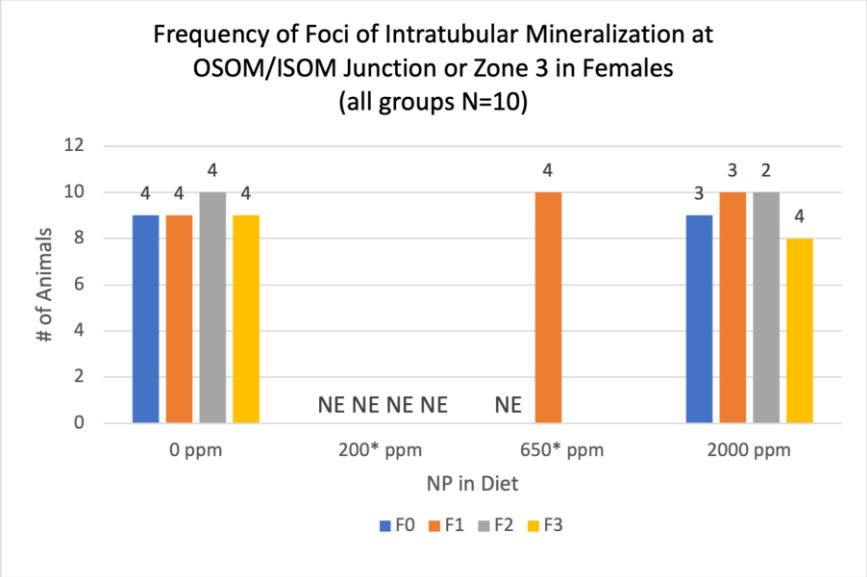
Figure 1: Kidney mineralization scores in male rats based on expert review by Hard



(1) Scores represent the highest score in each group. Scores for individual animals were not available.

[17] Hard, G.C. (1998). Expert Report on Renal Histopathologic Changes in Rat Dietary Studies with Nonylphenol Goldens Bridge NY, USA. Prepared for the Alkylphenols & Ethoxylates Research Council, Washington, DC, USA

Figure 2; Kidney mineralization scores in female rats based on expert review by Hard 1999 [(1), (2)]



(1) Scores represent the highest score in each group. Scores for individual animals were not available
(2) NTP 1997\Chapin, 1999 did not evaluate females the 200 ppm group and at 650 ppm only F1 was evaluated.

NE = not evaluated for mineralization as histopathologic slides were not prepared by NTP.

As illustrated in Figure 2 essentially all the histopathological changes in the kidney in male rats in the Chapin study, have been described as "slight to mild" with no indication of adversity as defined in the SONAR guidance. The exception was a score of 4 seen in the F0 650 ppm dose male group, which represents a very high dose of pNP. Also of particular note, is that the highest kidney mineralization scores in the female rats were all 4 for the female control group. Even with a high score of 4 for kidney mineralization, no adverse effects were noted in the control female rats, indicating that the mineralization did not affect the performance of the whole organism or reduce the organism's ability to respond to an additional environmental challenge.

Considering this, and that no functional changes in the kidney were seen in another 90-day rat toxicology study, and that no kidney weight changes were noted at the low doses in any of the studies, APERC's conclusion is that the kidney effects seen in male rats, in the Chapin, 1999 study, and the pNP dataset more broadly, are not adverse as defined in the SONARs for HRLs (2008, 2023).[18, 19]

In summary, it is important to keep in mind that all renal effects in young male rats in Chapin, 1999 were reported as slight to mild. [20]. Slight to mild histopathological findings related to

[18] Cunny. (1997).
[19] Chapin. (1999).
[20] Chapin. (1999).

kidney lesions in rats, which are generally viewed to have no pathologic significance, do not meet the level of "adverse" as defined in the SONARs for HRLs. [21, 22]

1.2.2 Renal mineralization in the Chapin, 1999 study was not accompanied by any other dose-related renal changes in the F2 male group, which was the group used by MDH to derive the POD for pNP.

In its response to APERC's comments on the subchronic and chronic HRLs for pNP, MDH justified its selection of renal mineralization as adverse because it "*might* be associated with renal degeneration" and "mineralization observed at the lowest dose *may* be a marker of more severe effects and *may* also be considered adverse."[23]

Table 1 shows the histopathology finding in the kidneys from male rats in the Chapin, 1999. All four generations of animals and the corresponding dose levels (ppm pNP in the diet) are presented. Although mineralization was present in males in all generations at the lowest dose, it was not accompanied by any other dose-related changes renal changes in the F2 male group, which was used in the BMDL modeling by MDH.

Table 1 Renal Effects in Generations of Male Rats (n=10, Table shows number of animals affected)

	F0				F1				F2				F3			
ppm	0	200	650	2000	0	200	650	2000	0	200	650	2000	0	200	650	2000
Renal Tubular Mineralization	0	3	3	4	1	4	7	7	0	5	9	10	0	4	9	6
Renal Tubular Casts	0	0	0	0	0	0	3	4	0	0	3	4	0	0	0	0
Renal Tubular Hydronephrosis	0	0	0	0	1	1	3	6	0	0	0	0	0	0	3	4
Renal Tubular Dilatation	0	0	0	0	0	0	0	0	1	2	1	7	1	5	10	8
Renal Tubular Cysts	0	0	0	0	0	0	0	0	1	2	1	5	1	4	10	8

No dose-related increase vs. controls
Dose-related increase vs. controls
Apparent increase vs. controls with problemmatic dose-response

1.3 MDH derived a POD for pNP based on an unreasonable interpretation of kidney mineralization in Chapin, 1999 as an adverse effect, this point-of-view is inconsistent with other governmental assessments of the same effect in the same study.

MDH has interpreted as "adverse" renal mineralization, a phenomenon that is widely recognized as common in rats. Background on this point was provided above and in APERC's previous comments.

[21] MDH. (2008, July 11).
[22] MDH. (2023, January 26).
[23] MDH. (2023, March 31)

Minnesota Statutes, section 144.0751, subdivision a, requires MDH to use "scientifically acceptable, peer-reviewed information" in deriving HRLs. Peer review ensures that the design and performance of the study meet scientific and technical standards and allows for a thorough critique of the study. The statute recognizes that governmental agencies also assemble and critically evaluate studies for the purpose of deriving a toxicity value such as a reference dose or slope factor. Once a governmental agency has derived a toxicity value from available data, the value is subject to review and constructive criticism by the scientific and risk assessment communities.

While APERC recognizes and respects the fact that MDH is not required to come to the same conclusions as other agencies, it is notable that five other authorities did not view the kidney effects in MDH's key study by NTP, 1997\Chapin, 1999 as adverse, especially at low doses. This was summarized in section 2.0 of the comments submitted by APERC on March 8th. The authorities cited were: US EPA (2009), US Dept of Agriculture, Forest Service (2003), Demark (2000), Environment and Health Canada (2001), and the European Chemicals Agency (ECHA), (2014). [24, 25, 26, 27,28]

In APERC's view MDH's conclusions regarding the kidney effects in rats diverges from the other authorities due to its unreasonable and singular misinterpretation of what signifies "adverse" in rat kidney studies.

> 1.4 It is APERC's view that MDH has not provided a reasonable justification for its interpretation of kidney mineralization as an "adverse" effect; MDH's conclusions regarding kidney mineralization are inconsistent with scientific guidance on the relevance of the mineralization in rats as well as the findings in the cited source study, and are not consistent with the SONAR definition of "adverse".

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[24] U.S. Environmental Protection Agency (US EPA), (2009, September) Screening Level Hazard Characterization Document: Alkylphenols Category. Developed under the High Production Volume Chemical Challenge. Link to Alkylphenols Summary Document

[25] Bakke, D. USDA Forest Service (2003, May). Human and Ecological Risk Assessment of Nonylphenol Polyethoxylate-based (NPE) Surfactants in Forest Service Herbicide Applications. https://www.fs.usda.gov/Internet/FSE_DOCUMENTS/stelprdb5346866.pdf Accessed March 2023

[26] Environment Canada and Health Canada (EC and HC). (2001). Priority substances list assessment report for nonylphenol and its ethoxylates. ISBN: 0-662-29248-0. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/nonylphenol/index-eng.php

[27] Canadian Council of the Ministers of the Environment (CCME) (2002) Canadian water quality guidelines for the Protection of Aquatic Life. Nonylphenol and its ethoxylates. https://ccme.ca/en/res/nonylphenol-and-its-ethoxylates-canadian-sediment-quality-guidelines-for-the-protection-ofaquatic-life-en.pdf Accessed March 2023

[28] European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) and Committee for Socioeconomic Analysis (SEAC). (2014, May 14), Background document to the Opinion on the Annex XV dossier proposing restrictions on Nonylphenol Ethoxylate. ECHA/RAC/ RES-O-0000005317-74-01/F 2014; Available from: https://www.echa.europa.eu/documents/10162/92b9634c-8d8e-4866-b9fe-11892e1fdc3

MDH has not demonstrated reasonableness for its reliance on an end point (kidney mineralization effects in male rats) as adverse for the selection of a Critical Effect for pNP. There is scientific consensus that rats are prone to have a high rate of these spontaneous kidney lesions. This was addressed in the presentation that Dr. Osimitz provided to MDH on Dec. 15, 2022. Furthermore, MDH has stretched the definition of "adverse" beyond what is defined in the SONAR guidance for deriving HRLs.

It is APERC's view that MDH did not provide a reasonable interpretation of "adverse" regarding renal mineralization in rats as it is inconsistent with scientific guidance on the relevance of the mineralization findings for pNP in rats, is inconsistent with the findings in the cited source study, and is not consistent with the SONAR definition of "adverse". [29, 30] SONAR defines "adverse effect" as "a biochemical change, functional impairment, or pathologic lesion that *affects* the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge." It does not say that effects that "*might* be associated" with another effect or "*may* be considered a marker" are adverse.

2.0 APERC Recommended Revisions to pNP subchronic and chronic, POD, RFDs and HRLs.

It is APERC's view that renal mineralization in male rats as seen in the Chapin, 1999 study does not meet the definition of an "adverse effect" as defined under in the SONARs for HRLs and it is therefore unreasonable to use this endpoint as the POD in calculating the subchronic and chronic HRLs for pNP. Rather, APERC recommends that MDH use the No Observable Adverse Effect Level (NOAEL) for acceleration of vaginal opening in female rats from the same study as the Critical Effect and POD in calculating the subchronic and chronic HRLs for pNP. Acceleration of vaginal opening is recognized as an adverse effect, a clear NOAEL is available for this endpoint in the Chapin, 1999 study and five other governmental authorities have selected this effect from the same study as the Critical Effect or POD for risk assessments.

TABLE 2: APERC Recommended Revisions to pNP Subchronic and Chronic RfDs and HRLs based on NOAEL for acceleration of vaginal opening in female rats in Chapin, 1999.

Recommended Reference Doses
Reference Dose/Concentration = HED/Total Uncertainty Factor (UF)

	Subchronic	**Chronic**
POD (mg/kg) (developmental\reproductive)	13	13
Dose Adjustment Factor (DAF)	0.25	0.25

[29] MDH. (2008, July 11).
[30] MDH. (2023, January 16).

Human Equivalent Dose (HED): POD x DAF (mg/kg)	**3.25**	**3.25**
Interspecies UF (TD)	3	3
Intraspecies UF	10	10
Subchronic to Chronic		3
Total uncertainty factor (UF)	**30**	**100**
Reference Dose (mg/kg)		0.0325

Recommended Health Based Values

Health Based Value = (Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor) (Subchronic Intake Rate, L/kg-d)

	Subchronic	**Chronic**
Reference Dose (mg/kg/day)	0.108	0.0325
Relative Source Contribution	0.2	0.2
Conversion Factor (1000 µg/mg)	1000	1000
Intake rate - L/kg/day	0.074	0.045
Health Based Value (µg/L)	**293**	**144**

Recognizing that MDL has discretion to use a Benchmark Dose (BMD) approach rather than a NOAEL to derive a POD for derivation of HRLs, APERC ran US EPA's BMD software (ver. 3.3.0) for the accelerated vaginal opening endpoint results seen in Chapin, 1999. [31] The LogProbit model was recommended as the best fitting model in the BMD output, since it had the lowest AIC [32] value of all of the models. The LogProbit gave a BMDL result of 224.468 ppm, which is equivalent to approximately 16 mg/kg-d. This modeled POD is slightly higher than the NOAEL of 200 ppm (13 mg/kg-d) pNP and would result in a higher HRL.

[31] U.S. EPA (2023, March 14) Benchmark Dose Software online. Version 3.3.0.. https://www.epa.gov/bmds/bmds-online

[32] The Akaike information Criterion (AIC) is most often used for model selection. By calculating and comparing the AIC scores of several possible models, you can choose the one that is the best fit for the data. The EPA states that "The model with the lowest AIC may be used to calculate the BMDL for the Point of Departure for risk assessment. This criterion is intended to help arrive at a single BMDL value in an objective, reproducible manner."

April 26, 2023

Barbara Losey, Executive Director
The Alkylphenols & Ethoxylates Research Council (APERC)
1250 Connecticut Avenue, NW
Suite 700
Washington, DC 20036

Re: Comments of the Alkylphenols & Ethoxylates Research Council
In the Matter of the Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Ch. 4717.7860 Subpart 13a p-Nonylphenol (4-Nonylphenol) (Discussion 38941)

Dear Barbara Losey:

In an April 26, 2023, post-hearing letter to the Minnesota Department of Health (MDH), the Alkylphenols and Ethoxylates Research Council (APERC) reiterates that the health effect that MDH based their nonylphenol guidance on (renal mineralization reported in young male rats from Chapin 1999[1]) is not adverse and is inconsistent with assessments by other governmental agencies. APERC states that the renal mineralization was described as "slight to mild" by the study pathologist and provides graphs that visually support that description. APERC further asserts that by basing guidance on renal mineralization (a non-adverse effect according to APERC), MDH is acting contrary to our 2008 SONAR[2]. MDH sincerely appreciates the post-hearing comments from APERC on our nonylphenol guidance and respectfully disagrees with APERC that 1) renal mineralization in the Chapin 1999 study is not adverse; and that 2) MDH is not acting in accordance with our 2008 SONAR.

First, MDH emphasizes that the adverse effect, renal mineralization, is occurring in young male rats that were exposed to nonylphenol *in utero* and through lactation. The occurrence in young male rats is the key. This is a rare occurrence. Although renal mineralization was scored as "slight to mild" in the Chapin study, the incidence of this effect was observed in three different generations of rats at the lowest dose tested, and the incidence increased with increasing doses. Because this study was designed to capture developmental and early life health effects, the animals were not kept into adulthood. Renal mineralization is most often seen in adult animals as it can occur as part of normal aging in laboratory rodents. It is likely that if the animals were followed into adulthood, the level of renal mineralization would increase, indicating more severe kidney damage. Again, the fact that this effect was seen in young animals was concerning. In concordance with MDH, this effect was also identified as an adverse effect in a European Union risk assessment[3].

APERC is correct in that our 2008 SONAR does cite EPA's definition of an adverse effect as "a biochemical change, functional impairment, or pathological lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge".

However, our 2008 SONAR also states that "in order for an effect to serve as the basis for an MDH-derived HRL, it must be adverse, or a *precursor to an adverse effect*" (p27 MDH 2008, emphasis added). Therefore, whether renal mineralization is a marker for renal degeneration, as stated in the National Toxicology Program (NTP) Non-neoplastic Lesion Atlas[4], also cited by APERC, or whether a longer nonylphenol exposure would have produced a score more severe than "slight to mild" in these rats, both are considered adverse according to MDH's 2008 SONAR.

MDH respectfully concludes that renal mineralization is an adverse effect and follows the guidance in our 2008 SONAR.

Sincerely,

Sarah Fossen Johnson, PhD
Manager, Environmental Surveillance and Assessment Section
Minnesota Department of Health
Environmental Health Division
health.risk@state.mn.us-
www.health.state.mn.us

References

[1]Chapin, RE *et al*. (1999). The Effects of 4-nonylphenol in Rats: A Multigeneration Reproduction Study. *Toxicol Sci*, 52(1), 80-91.

[2] Minnesota Department of Health Statement of Need and Reasonableness (SONAR). (2008). https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=2

[3]European Chemicals Bureau (2002). European Union Risk Assessment Report for 4-nonylphenol (Branched) and Nonylphenol. https://echa.europa.eu/documents/10162/6c460d8a-9f18-475f-823c-b8941e18fa3a

[4]National Toxicology Program (NTP). Nonneoplastic Lesion Atlas. https://ntp.niehs.nih.gov/nnl/

L.1.d. Written Comment: Post-Hearing Comments- Imidacloprid

L.1.d.i. Comment
Date: April 26, 2023
Chemicals: Imidacloprid
Commenter: Bayer Crop Science

L.1.d.ii. Minnesota Department of Health's Preliminary Response
Date: April 26, 2023

April 26, 2023

Nancy Rice
Minnesota Department of Health
Robert Street North
P.O. Box 64975
St. Paul, MN 55164-0975

RE: Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, and Part 7860; Revisor's ID Number RD4587, OAH Docket No. 5-9000-38941

Thank you for the opportunity to provide public input on the Minnesota Department of Health's (MDH's) proposed groundwater health risk limit for imidacloprid. Bayer Crop Science produces several products that rely on imidacloprid as an active ingredient to control insect pests. Bayer previously submitted written comments on the proposed groundwater health risk limit on March 8, 2023, and received the MDH's response letter, dated March 31, 2023[1].

In its response letter to Bayer, MDH stated, "The purpose of risk assessment is different between EPA and MDH. EPA's role is to register pesticides, MDH's role is to derive water guidance that is protective, including a margin of safety, for sensitive and highly exposed individuals in the general population." This statement mischaracterizes the purpose of EPA's risk assessments. When EPA considers aggregate human exposures resulting from drinking water, food, and residential exposures, it may only approve uses where it can conclude there is a "reasonable certainty of no harm."[2] EPA's "reasonable certainty of no harm" standard applies to infants, children, and other potentially-sensitive populations, with additional safety factors that EPA must apply by default unless sufficient data and information are available to demonstrate additional safety factors are not necessary. This is a high standard and is consistent with MDH's mission to protect public health.

In response to Bayer's comment that Badgujar et al. (2013)[3], the study MDH relied on to calculate the proposed health risk limit for imidacloprid, is missing key information that would allow it to inform a quantitative risk assessment, MDH stated, "It is unusual in the open

[1] https://www.health.state.mn.us/communities/environment/risk/docs/rules/comments/mdhbayerresp.pdf
[2] EPA. 2022. Summary of the Federal Food, Drug, and Cosmetic Act. https://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act
[3] Badgujar, P.C., et al. 2013. Immunotoxic effects of imidacloprid following 28 days of oral exposure in BALB/c mice. Environmental Toxicology and Pharmacology. 35:408-418. doi: 10.1016/j.etap.2013.01.012

literature for academic peer-reviewed studies to include raw data, and minute study details, due to journal article space and word number constraints." In fact, scientific journals, including the journal that published Badgujar et al. (2013), allow authors to include additional data with the digital version of the publication to "validate research findings".[4] Nevertheless, the authors of the publication MDH relied on to calculate the proposed groundwater health risk limit for imidacloprid did not provide additional data or details in any form that readers could use to evaluate whether the publication's conclusions accurately reflect the raw data. MDH could contact the study authors to request the raw data and conduct its own review to establish whether the raw data support the study's conclusions.

In response to Bayer's comment that a valid, guideline compliant study conducted according to Good Laboratory Practices (GLPs) is available and is of higher quality than the study MDH relied on, MDH stated, "While it is true that industry uses GLP and follows EPA's Immunotoxicity Guidelines (EPA 1998), academia in the open literature uses peer-review and journal editors to assess the quality of their work." In fact, GLP regulations and peer review are not equivalent. GLP regulations enable thorough reviews not only of the data but also the qualifications of the people who conducted the study, the full chemical identity of the test material, calibration records for all laboratory equipment, and rigorous documentation of study conditions.[5] The quality of an individual peer review is specific to the people who conducted it and the amount of time and information they had available. Completing peer review does not establish that one study is of similar quality or reliability as another study conducted in compliance with GLP regulations according to internationally accepted guidelines.

To support its position that EPA's human exposure limit for imidacloprid is not sufficient to protect human health, MDH stated, "Furthermore, both the State of Wisconsin and The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) have stated that EPA's RfD for imidacloprid is not health protective." Authoritative bodies in Wisconsin and California responsible for regulating pesticides have affirmatively rejected groundwater standards that stem from analyses that conflict with EPA's human health risk assessment. Wisconsin's Department of Natural Resources reviewed the proposed imidacloprid groundwater standard that MDH cites and voted not to adopt it in February 2022[6]. In its review of OEHHA's assessment, the Human Health Assessment Branch of California's Department of Pesticide Regulation (DPR) "determined that several of the studies

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[4] Elsevier Publishing. 2023. Environmental Toxicology and Pharmacology instructions for authors: Research Data. https://www.elsevier.com/journals/environmental-toxicology-and-pharmacology/1382-6689/guide-for-authors

[5] EPA. 2022. Good Laboratory Practices Standards Compliance Monitoring Program. https://www.epa.gov/compliance/good-laboratory-practices-standards-compliance-monitoring-program

[6] https://widnr.widen.net/view/pdf/icborcvkrw/2022-02-APPROVED-February-Brief-of-Action.pdf?t.download=true&u=2ge66j ("At 4:47:05, the motion to approve item 4.C. Board Order DG-15-19 failed on a roll call vote of 3-3")

cited by OEHHA had experimental design, reporting, or statistical issues that precluded their use as the basis for a regulatory action."[7] OEHHA's analysis included Badgujar et al. (2013) that MDH seeks to use as the basis of Minnesota's proposed health risk limit for imidacloprid. In other words, California DPR reached a similar conclusion as EPA – that Badgujar et al. (2013) is not reliable for use in a quantitative risk assessment.

Choosing a single, low-quality study (Badgujar et al., 2013) as the basis for MDH's assessment does not satisfy the "reasonableness" requirements that the Minnesota Administrative Procedure Act (APA), Minnesota Statutes, Chapter 14 describes. Recent regulatory reviews of imidacloprid at the federal (EPA) and state (California DPR) levels have specifically considered Badgujar et al. (2013) and found that it is not suitable for quantitative risk assessment. MDH's response to Bayer's original comments do not provide any basis for relying on Badgujar et al. (2013) beyond that it examined the effects of imidacloprid on the immune system of female mice and that it appeared in a peer-reviewed journal.

A higher quality study (Kennel, 2010), conducted according to internationally accepted methods, in compliance with GLP standards, is available and serves as the basis of EPA's current human health risk assessment with respect to immunotoxicity. There is no basis to conclude that the results that Badgujar et al. (2013) present accurately reflect the underlying raw data – one of several reasons EPA chose not to rely on this publication in its most recent risk assessments. Absent an independent review of the raw data against the conclusions, there is no way to know how reliable Badgujar et al. (2013) is and there is no way to establish that it is sufficiently reliable to serve as the basis for quantitative risk assessment.

Best regards,

William R. Reeves, Ph.D.
Regulatory Scientific Affairs
Bayer U.S. LLC Crop Science Division
700 Chesterfield Parkway West
Chesterfield, MO 63017
Tel. +1 314 807 0974
william.reeves@bayer.com

[7] CDPR. Subcommittee of the Pesticide Registration and Evaluation Committee; Implementation of the Pesticide Contamination Prevention Act; Imidacloprid: Subcommittee Findings and Recommendations May 17, 2022. https://www.cdpr.ca.gov/docs/emon/grndwtr/imidacloprid/prec_findings_recommendations.pdf

April 26, 2023

William R. Reeves, Ph.D.
Regulatory Scientific Affairs
Bayer U.S. LLC Crop Science Division
700 Chesterfield Parkway West
Chesterfield, MO 63017

Re: Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, and Part 7860; Revisor's ID Number RD4587, OAH Docket No. 5-9000-38941

Dear William Reeves:

In an April 26, 2023 post-hearing comment to MDH, Bayer Crop Sciences reiterates that the Minnesota Department of Health (MDH) relied on an immunotoxicity study (Badgujar 2013[1]) that is missing key information that would allow it to inform a quantitative risk assessment for imidacloprid. They promote the use of a different registrant-sponsored study (Kennel 2010[2]) as the appropriate immunotoxicity study for imidacloprid. Bayer argues that the Kennel 2010 study did not show any immune response in animals after imidacloprid exposure. MDH respectfully disagrees with Bayer's conclusions.

MDH selected a peer-reviewed immunotoxicity study (Badgujar 2013) that reported reduced delayed-type hypersensitivity in female mice. There was a strong dose-response alongside the correct controls. MDH was able to conduct an appropriate risk analysis based on this study. MDH also analyzed the data in Kennel 2010, supplied by Bayer Crop Sciences. Kennel focused on a different arm of the immune system (IgM titers in the serum after antigen challenge) in a different species (rat) that produced data with high standard deviations. Despite this high variability, MDH believes that there is, in fact, evidence of a reduction in IgM after imidacloprid treatment in treated animals, but because of the study limitations, statistical significance was not achieved.

MDH thanks Bayer Crop Sciences for sharing Kennel 2010 with MDH. Although Kennel 2010 was conducted under Good Laboratory Practices (GLP), it was not available to the public or public agencies prior to MDH's proposed imidacloprid guidance. MDH agrees with Bayer Crop Sciences that GLP regulations and peer review are not equivalent. Bayer writes in their comments that "GLP regulations enable thorough reviews not only of the data but also the qualifications of the people who conducted the study, the full chemical identity of the test

material, calibration records for all laboratory equipment, and rigorous documentation of study conditions". Much of GLP is directives for excellent record keeping. Peer review is scrutiny of the data and the conclusions of a study, once the study is completed. MDH's 2008 SONAR[3] requires peer-reviewed studies as the basis for developing guidance as spelled out in Minnesota Statute section 144.0751[4]. There is not a requirement for GLP.

There is also no requirement for other states to approve a chemical in order for MDH to calculate health-based water guidance values. The citation and link provided by Bayer that claims the Wisconsin DNR disproving of their imidacloprid value is dubious, at best. When you search the article, the word imidacloprid is not found. Perhaps there was some action, but it is not clear from documentation shown. Additionally, it is not actually the Wisconsin DNR, it is the Wisconsin Natural Resources Board, a policy group. There isn't a single toxicologist or risk assessor on the board, rather it is led by people with administrative and business backgrounds. Some of the members have a science background that is appropriate for natural resources management such as deer culls. Health-based values are derived using toxicological and risk assessment principles, very specific knowledge that is difficult to critique for those who are not trained. In addition, California's Office of Environmental Health Hazard Assessment (OEHHA), is still reviewing imidacloprid. There is no mention of imidacloprid in the citation or link supplied by Bayer Crop Sciences.

Lastly, MDH would like to emphasize that HRLs are developed to protect the health of all Minnesotans. MDH conducted a thorough analysis of the imidacloprid database including documents produced by EPA. MDH maintains that the purpose of MDH and EPA are different. While MDH produces HRLs that are health-based, EPA reviews pesticides through a registration lens. In EPA's website, "Why We Review Pesticides" EPA states that "EPA…reviews pesticides to ensure they can be used safely, without unreasonable risks to human health and the environment[5]." *Unreasonable risk*. This is the purpose: to register pesticides for use. It is not specifically to protect human health, as MDH risk assessments are. It follows that the "reasonable certainty of no harm" is a different standard than protecting all Minnesotans, including those most sensitive or most highly exposed. Every risk assessment at MDH begins with the aim of protecting every Minnesotan. That is a different approach than a 'reasonable certainty.

In conclusion, MDH is confident in the selection of Badgujar 2013 as the critical study for imidacloprid. This selection provides protection of imidacloprid exposure to the most highly sensitive or most highly exposed Minnesotans.

Sincerely,

/s/Sarah Johnson

Sarah Fossen Johnson, PhD
Manager, Environmental Surveillance and Assessment Section
Minnesota Department of Health
Environmental Health Division
651-201-4899
health.risk@state.mn.us-
www.health.state.mn.us

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[4]Minnesota Statutes. (2022). Health Standards. 144.0751. https://www.revisor.mn.gov/statutes/cite/144.0751

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